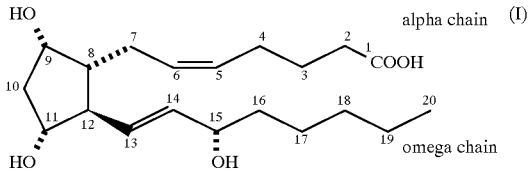
USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

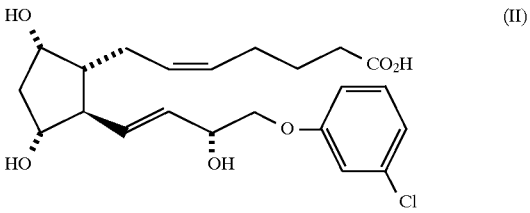
The present application is a continuation of U.S. patent application Ser. No. 08/769,293, filed Dec. 18, 1996, now U.S. Pat. No. 5,665,773, which is a continuation of U.S. patent application Ser. No. 08/280,681, filed Jul. 26, 1994, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 08/101,598 filed Aug. 3, 1993 now U.S. Pat. No. 5,510,383.

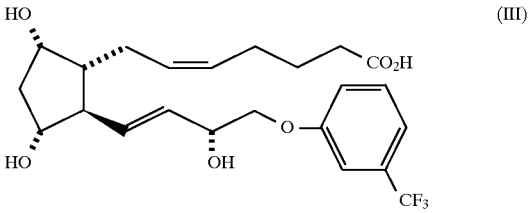
BACKGROUND OF THE INVENTION

The present invention relates to the treatment of glaucoma and ocular hypertension. In particular, the present invention relates to the use of cloprostenol and fluprostenol analogues for the treatment of glaucoma and ocular hypertension.

Cloprostenol and fluprostenol, both known compounds, are synthetic analogues of $PGF_{2\alpha}$, a naturally-occurring F-series prostaglandin (PG). Structures for $PGF_{2\alpha}$ (I), cloprostenol (II), and fluprostenol (III), are shown below:







The chemical name for cloprostenol is 16-(3-chlorophenoxy)-17,18,19,20-tetranor $PGF_{2\alpha}$. Monograph No. 2397 (page 375) of *The Merck Index,* 11th Edition (1989) is incorporated herein by reference to the extent that it describes the preparation and known pharmacological profiles of cloprostenol. Fluprostenol has the chemical name 16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor $PGF_{2\alpha}$. Monograph No. 4121 (pages 656–657) of *The Merck Index,* 11th Edition (1989) is incorporated herein by reference to the extent that it describes the preparation and known pharmacological profiles of fluprostenol. Cloprostenol and fluprostenol are 16-aryloxy PGs and, in addition to the substituted aromatic ring, differ from the natural product $PGF_{2\alpha}$, in that an oxygen atom is embedded within the lower (omega) chain. This oxygen interruption forms an ether functionality.

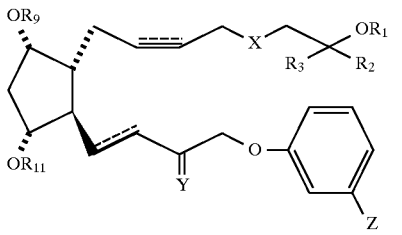
Naturally-occurring prostaglandins are known to lower intraocular pressure (IOP) after topical ocular instillation, but generally cause inflammation, as well as surface irritation characterized by conjunctival hyperemia and edema. Many synthetic prostaglandins have been observed to lower intraocular pressure, but such compounds also produce the aforementioned side effects which severely restrict clinical utility.

SUMMARY OF THE INVENTION

It has now been unexpectedly found that certain novel cloprostenol and fluprostenol analogues are useful in treating glaucoma and ocular hypertension. In particular, topical application of ophthalmic compositions comprising these novel cloprostenol and fluprostenol analogues result in significant IOP reduction.

DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the present invention have the following general formula:



(IV)

wherein:

R_1=H; C_1–C_{12} straight-chain or branched alkyl; C_1–C_{12} straight-chain or branched acyl; C_3–C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3 =H, or C_1–C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X=O, S, or CH_2;

- - - represents any combination of a single bond, or a cis or trans double bond for the alpha (upper) chain; and a single bond or trans double bond for the omega (lower) chain;

R_9=H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

R_{11} =H, C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl;

Y=O; or H and OR_{15} in either configuration wherein R_{15}=H. C_1–C_{10} straight-chain or branched alkyl, or C_1–C_{10} straight-chain or branched acyl; and

Z=Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$–C_{12} straight-chain or branched acyl; and when R_2 =R_3 =H, then $R_1 \neq$a cationic salt moiety.

As used herein, the term "cationic salt moiety" includes alkali and alkaline earth metal salts as well as ammonium salts.

Preferred compounds include the 3-oxa form of cloprostenol isopropyl ester (Table, 1, compound 5), 13,14-dihydrofluprostenol isopropyl ester (compound 6), cloprostenol-1-ol (compound 7), and 13,14-dihydrocloprostenol-1-ol pivaloate (compound 8).

The compounds of formula (IV) are useful in lowering intraocular pressure and thus are useful in the treatment of glaucoma. The preferred route of administration is topical. The dosage range for topical administration is generally between about 0.01 and about 1000 micrograms per eye (μg/eye), preferably between about 0.1 and about 100